Studies on the Synthesis of Heterocyclic Compounds. II. Synthesis of 2,2-Disubstituted-1,3-benzoxathioles (1).

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The condensation of 2-hydroxythiophenol (I) with acetylenic compounds (IIa-g) or halogenated esters (IV, V, VIa and b) led to the synthesis of 2,2-disubstituted-1,3-benzoxathioles (IIIa-g). The structures of these compounds were established by elemental analysis and by ir and nmr spectra.

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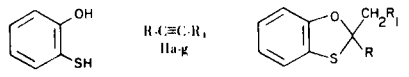
It has previously been shown (2) that the reaction of 2-hydroxythiophenol with aldehydes or ketones yields 2-alkyl- and 2-aryl-substituted-1,3-benzoxathioles, while with α-bromo-β-alkylolefinic esters or nitriles 1,4-benzoxathians are obtained (3). The synthesis of 2-carboalkyl- and 2-carboxyalkyl-substituted-1,3-benzoxathioles has not been fully investigated (4).

In order to study the possibility of obtaining 1,3-benzoxathioles or 1,4-benzoxathians or mixtures of them, we have examined in the present paper the reaction of 2-hydroxythiophenol (I) with acetylenic compounds (IIa-g).



I IIIa-m

a, R = C_6H_5, R_1 = CO_2Me
b, R = R_1 = CO_2Me
c, R = H, R_1 = CO_2Et
d, R = CH_3, R_1 = CO_2Et
e, R = C_6H_5, R_1 = $COCH_3$
f, R = C_6H_5, R_1 = H
g, R = C_6H_5, R_1 = CH_3
h, R = C_6H_5, R_1 = CO_2H
i, R = R_1 = CO_2H
l, R = H, R_1 = CO_2H
m, R = CH_3, R_1 = CO_2H

All the reactions have been performed in the presence of potassium carbonate or sodium ethoxide. On the basis of our results we have found that only 1,3-benzoxathioles (IIIa-g) are obtained.

The formation of 1,3-benzoxathioles can be rationalized mechanistically by a series of Michael additions (5) involving 2-hydroxythiophenol (Scheme 1). A nucleophilic attack of the thiophenoxide anion on the β-carbon atom would yield intermediate "A". A second nucleophilic attack on the β-carbon atom would give the desired 1,3-benzoxathiole. This fact is supported by the isolation of the intermediate "A" (R = R_1 = CO_2Me) in the reaction of I with IIb; from "A" 1,3-benzoxathiole IIIb is easily obtained. In these reactions we have never observed the formation of 2-benzyl derivatives; the balance was the starting materials.

In contrast to the inability to form 1,3-benzodioxoles from unactivated acetylenes and 1,2-dihydroxybenzene (6), we noted the formation of 1,3-benzoxathiolic compounds when I is treated with acetylenic compounds having the triple bond not activated by a conjugation with groups having a -M effect. From our results it can be seen that ethynylbenzene (IIf) as well as (1-propynyl)benzene (IIg) gave, although in rather low yields, the corresponding derivatives III (f and g). This can be justified considering that the thiophenoxide anion can attack also the non-activated triple bond, because of the greater nucleophilicity of sulfur and the greater acidity of thiophenols (7).

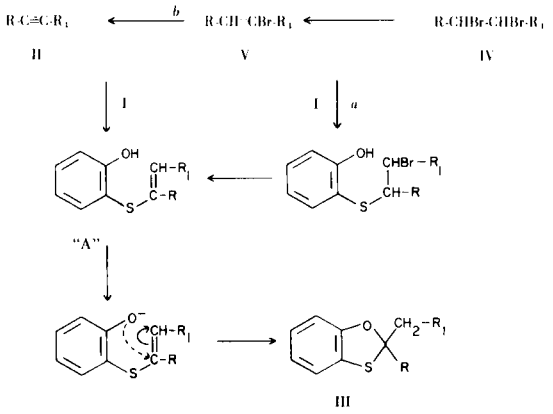
In order to obtain 1,4-benzoxathians, the reactions have been extended to the halogenated esters IV, V, VI (a and b), that in contrast to those already investigated (3,8) bear β-phenyl or β-carboxyl- groups.

R-CHBr-CHBr-R_1 R-CH=CBr-R_1 R-CBr=CBr-R_1
IVa-b Va-b VIa-b

a, R = C_6H_5, R_1 = CO_2Me
b, R = R_1 = CO_2Me

In this case only the 1,3-benzoxathioles IIIa-b have been

Scheme I



obtained.

The results obtained from saturated dibromoderivatives (IVa-b) can be explained with a mechanism (path *a*) involving a dehydrohalogenation of IVa-b to give Va-b; these monobromoalkenes could give the heterocyclic compound by a Michael reaction on I followed by the closure of the ring (3) (Scheme I). In fact, from the reaction medium both the monobromoalkenes V (a and b) were also isolated (yield 15-20%), that gave 1,3-benzoxathioles IIIa-b in the reaction with I. On the other hand, we can not exclude a different pathway (path *b*) that would involve another dehydrohalogenation of Va-b to give IIa-b, that could react by the above mechanism. We have noticed in fact that the compounds Va-b give the corresponding acetylenic compounds IIa-b, although in low yields (10-15%), when they react with potassium carbonate or sodium ethoxide for a long time (50 hours).

Also in these reactions we have never observed the formation of 2-benzyl derivatives.

When we performed the reactions with alkenic dibromoderivatives (VIa-b) we obtained the same 1,3-benzoxathioles

Scheme II

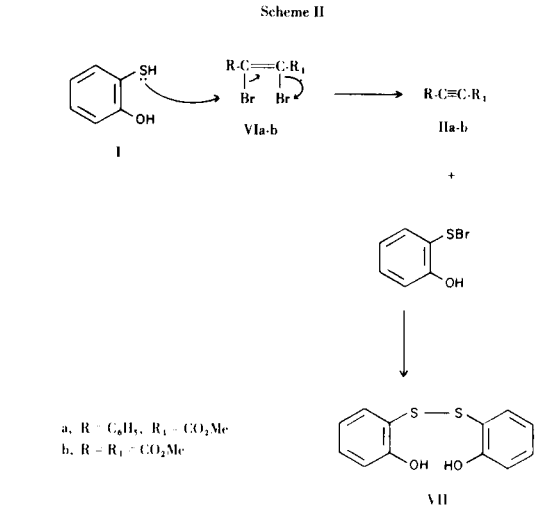


Table I

Condensation of 2-Hydroxythiophenol (I) with Acetylenic Compounds (IIa-g)

Acetylenic Compound	Product	Method of Preparation	Yield %
IIa (a)	IIIa	A	51
		B	27
IIb (b)	IIIb	A	42
		B	30
IIc (b)	IIIc	A	45
		B	30
IId (c)	IIId	A	48
		B	31
IIe (b)	IIIe	A	50
		B	42
IIf (b)	IIIf	A	4 (d)
		B	10
IIg (b)	IIIg	A	3 (d)
		B	12

(a) Reference (12). (b) Available from Aldrich Chemical Company. (c) Reference (13). (d) Compound not isolated, yield determined by glc.

Table II

Condensation of 2-Hydroxythiophenol (I) with Halogenated Esters (III, IV and V)

Halogenated Ester	Product	Method of Preparation	Yield %
IVa (a)	IIIa	A	55
		B	61
Va (b)	IIIa	A	58
		B	63
VIa (c)	IIIa	A	44
		B	46
IVb (d)	IIIb	A	40
		B	47
Vb (e)	IIIb	A	45
		B	49
VIb (f)	IIIb	A	38
		B	47

(a) Reference (14). (b) Reference (15). (c) Reference (16). (d) Reference (17). (e) Reference (18). (f) Reference (19).

(IIIa-b) and 2,2'-dithiobisphenol (VII). In this case, presumably, VIa-b are reduced to IIa-b by the 2-hydroxythiophenol moiety (Scheme II). In a second step II (a and b) could react with I to yield IIIa-b.

On the other hand, attempts to obtain 2-phenyl-2-

Table III

2,2-Disubstituted-1,3-benzoxathioles (VIa-g)

Compound	M.p. °C	B.p./mm	Empirical Formula	Calcd. % C	Calcd. % H	Calcd. % S	Found % C	Found % H	Found % S
IIIa	55-56 (a)		$C_{16}H_{14}O_3S$	67.11	4.93	11.20	67.21	4.81	11.10
IIIb	52 (a)	173-175/1.5	$C_{12}H_{12}O_5S$	53.72	4.51	11.95	53.83	4.60	11.83
IIIc		148-150/2 (b)	$C_{11}H_{12}O_3S$	58.91	5.40	14.29	58.80	5.35	14.10
IIId		151-152/2 (c)	$C_{12}H_{14}O_3S$						
IIIe	54 (a)		$C_{16}H_{14}O_2S$	71.08	5.22	11.86	70.92	5.30	11.73
IIIf		155-156/2 (d)	$C_{14}H_{12}OS$						
IIIg		167-168/2 (e)	$C_{15}H_{14}OS$						

(a) Recrystallized from diisopropyl ether. (b) n^{19}_D 1.5570. (c) Lit. (Reference 4) b.p. 163-165° (4 mm). (d) Lit. (Reference 20) b.p. 148-150° (1 mm). (e) Lit. (Reference 2) b.p. 159-160° (1 mm).

Table IV

2,2-Disubstituted-1,3-benzoxathioles (IIIh-m and XIa-b)

Compound	Yield %	M.p. °C	B.p./mm	Empirical Formula	Calcd. % C	Calcd. % H	Calcd. % S	Found % C	Found % H	Found % S
IIIh	84	142-143 (a)		$C_{15}H_{12}O_3S$	66.16	4.44	11.77	66.10	4.37	11.65
IIIi	80	103-105 (b)		$C_{10}H_8O_5S$	49.99	3.36	13.35	49.85	3.28	13.24
IIIl	88	150-151 (a)		$C_9H_8O_3S$	55.09	4.11	16.34	55.06	4.12	13.27
IIIm	78	145-146 (c)		$C_{10}H_{10}O_3S$						
XIa	91		198-200/2 (d)	$C_{15}H_{14}O_2S$	69.74	5.46	12.42	69.70	5.38	12.31
XIb	88		181-182/4 (e)	$C_{16}H_{16}O_2S$	70.56	5.92	11.77	70.44	5.84	11.63

(a) Recrystallized from benzene. (b) Recrystallized from chloroform. (c) Lit. (Reference 4) m.p. 145-147°. (d) n^{28}_D 1.6160. (e) n^{19}_D 1.6017.

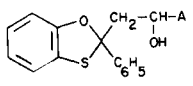
benzyl-1,3-benzoxathiole or 2,3-diphenyl-1,4-benzoxathiane by treating I with diphenylacetylene (VIII) as well as with α,α′-dibromobibenzyl (IX) were unsuccessful. In fact in the first case we found the starting material, while in the second case the compound IX gave *trans*-stilbene (X) and I was converted to VII. We can attribute the inability to form the desired products to the steric hindrance of the two phenyl groups.

The structures of all the prepared compounds were established by their elemental analysis, ir and nmr spectra. The compounds IIIa and IIIe are 2-phenyl and not 2-benzyl derivatives because they give by reduction the alcohols XIa and XIb, respectively, whose nmr spectra show a multiplet at δ 2.80-2.55 attributable to the methylenic protons adjacent to the alcoholic group.

C_6H_5-C≡C-C_6H_5 C_6H_5-CHBr-CHBr-C_6H_5 C_6H_5-CH=CH-C_6H_5

VIII IX X

a. A = H
b. A = CH_3



XIa-b

EXPERIMENTAL

The infrared spectra were obtained on a Perkin-Elmer model 325 spectrophotometer using either potassium bromide mulls or neat liquids between sodium chloride plates. Nmr spectra were determined on a Varian HA spectrometer working at 100 MHz and using hexamethyldisiloxane as internal standard. Gas chromatographic analyses were performed on a Carlo Erba GV instrument equipped with SE-30 column (2m x 0.5 cm., 10% on carbowax 20M). Microanalyses for CHN were carried out on a Perkin-Elmer model 240 Elemental Analyzer; analyses for S were performed by the literature procedure (9). Melting points were uncorrected and obtained on a Tottoli apparatus. All boiling points were uncorrected and obtained from distillation or with a boiling point apparatus.

2-Hydroxythiophenol (I).

This compound was obtained, as previously reported, by diazotization of 2-hydroxyaniline (10,11), yield 80%, b.p. 101-102° (10 mm) [lit. (11), b.p. 105-107° (15 mm)].

General Methods for the Preparation of 1,3-Benzoxathioles (IIIa-g). Method A.

A mixture of I (0.08 mole), anhydrous potassium carbonate (0.155 mole) and dry acetone (80 ml.) was refluxed under a stream of nitrogen for 8 hours. To this suspension the appropriate

Table V

Spectrophotometric Data of 2,2-Disubstituted-1,3-benzoxathioles (IIIa-m and XIa-b)

Compound	Ir		Nmr (a)	
	cm^{-1}	ν	δ	Assignment
IIIa	1730	C=O	3.35	(s, 2, $-CH_2-CO_2-$)
			3.45	(s, 3, $-CO_2-CH_3$)
			7.10	(m, 9, Ar-H)
IIIb	1740	C=O	3.70	(s, 2, $-CH_2-CO_2-$)
			3.75	(s, 6, $-CO_2-CH_3$)
			6.85	(m, 4, Ar-H)
IIIc	1740	C=O	1.50	(t, 3, $-CH_3$)
			3.20	(m, 2, $-CH_2-CO_2-$)
			4.35	(q, 2, $-CH_2-O-CO-$)
			6.50	(t, 1, $-\underset{\vert}{C}H-$)
			7.10	(m, 4, Ar-H)
IIId (b)				
IIIe	1730	C=O	1.95	(s, 3, $-CO-CH_3$)
			3.45	(s, 2, $-CH_2-CO-$)
			7.10	(m, 9, Ar-H)
IIIf (c)				
IIIg (d)				
IIIh	3415	OH	3.35 (e)	(s, 2, $-CH_2-CO_2-$)
	1705	C=O	7.10	(m, 9, Ar-H)
			7.40	(s, 1, $-CO_2H$)
IIIi	3000	OH	3.75 (e)	(s, 2, $-CH_2-CO_2-$)
	1720	C=O	6.90	(m, 4, Ar-H)
			7.50	(s, 2, $-CO_2H$)
IIIl	3410	OH	3.25 (e)	(m, 2, $-CH_2-CO_2-$)
	1700	C=O	6.60	(t, 1, $-\underset{\vert}{C}H-$)
			7.10	(m, 4, Ar-H)
			7.45	(s, 1, $-CO_2H$)
IIIm (b)				
XIa	3380	OH	2.80	(t, 2, $-CH_2-CH_2OH$)
			3.60	(s, 1, -OH)
			3.85	(t, 2, $-CH_2-CH_2OH$)
			7.15	(m, 9, Ar-H)
XIb	3440	OH	1.10	(m, 3, $-CH_3$)
			2.40	(s, 1, -OH)
			2.55	(m, 2, $-CH_2-$)
			3.95	(m, 1, $-\underset{\vert}{C}H-$)
			7.15	(m, 9, Ar-H)

(a) Carbon tetrachloride solution unless otherwise noted. Signals are designated as follows: s, singlet; t, triplet; q, quartet; m, multiplet. (b) Reference (4). (c) Reference (20). (d) Reference (2). (e) DMSO-d_6 solution.

reactant (acetylenic, dibromo or monobromo compounds) (0.08 mole) was added and the mixture was refluxed for 50 hours under nitrogen. After the acetone was removed *in vacuo* (rotary flash evaporator, at 18-20 mm), the residue was poured into water (200 ml.) and extracted with chloroform. The extract was washed (in turn) with 10% aqueous sodium hydroxide, water and dried over anhydrous sodium sulfate. After solvent evaporation *in vacuo*, the crude product was chromatographed on a silica gel column, using petroleum ether-diethyl ether (3:1) as eluent.

The basic parts were treated with 10% sulfuric acid, extracted with diethyl ether and dried over sodium sulphate. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column using petroleum ether-diethyl ether (1:1) as eluent. Evaporation of the solvent furnished unreacted I.

In the reaction with IIb another product was also eluted, which was identified as *o*-(1,2-dicarbomethoxyvinylthio)phenol ("A": R = R_1 = CO_2Me), yield 15%, m.p. 134-135°; ir (potassium bromide): 3410 (OH), 1725 (C=O) and 1670 cm^{-1} (>C=C<); nmr (deuteriochloroform): δ 3.85 (s, 6 H, $-CO_2CH_3$), 6.90 (s, 1 H, OH, deuterium oxide exchanged) and 7.20 ppm (m, 4 H arom and 1 H, >C=CH-).

Anal. Calcd. for $C_{12}H_{12}O_5S$: C, 53.72; H, 4.51; S, 11.95. Found: C, 53.44; H, 4.46; S, 11.67.

This compound, treated with anhydrous potassium carbonate in dry acetone or with sodium ethoxide in absolute ethanol, furnished IIIb in 90% yield.

The basic parts of the reaction with VIa-b gave also a viscous yellow oil, which was identified as 2,2'-dithiobisphenol (VII) in equimolar amount with respect to IIIa-b, b.p. 151-152° (0.5 mm) [lit. (10), b.p. 160-170° (2 mm)].

Method B.

To a stirred solution of sodium ethoxide (0.122 mole, prepared from 2.8 g. of sodium) in absolute ethanol (75 ml.) under an atmosphere of nitrogen, I (0.122 mole) in absolute ethanol (30 ml.) was added dropwise. After stirring under reflux for 1.5 hours, the reactant [acetylenic (0.061 mole), dibromo or monobromo compounds (0.122 mole)] was added to this suspension and the mixture was refluxed for 35-40 hours. The solvent was then removed in a rotary evaporator and the residue was poured into water (200 ml.) and worked up as in Method A.

Melting or boiling points, yields, analytical data and physical properties of the products are summarized in Tables I, II, III and V.

Reaction of I with α,α'-Dibromobibenzyl.

A suspension of I (0.01 mole), anhydrous potassium carbonate (0.02 mole) in dry acetone (100 ml.) was refluxed (stirring) under a stream of nitrogen for 10 hours; the α,α'-dibromobibenzyl (IX) (21) (0.01 mole) was then added to the reaction mixture and the suspension was refluxed for 50 hours under nitrogen. After the acetone was removed *in vacuo*, the residue was poured into water and extracted with diethyl ether. The extracted was washed (in turn) with 10% aqueous sodium hydroxide, water and dried over anhydrous sodium sulphate. After solvent evaporation, the crude product, which was identified as *trans*-stilbene (X), crystallized from ethanol, yield 71%, m.p. 123-124°, and gave no depression in mixture melting point determination with an authentic sample of commercial product.

The basic parts were treated with 10% sulfuric acid, extracted with diethyl ether and distilled to give VII, yield 78%.

The same results were obtained performing the reaction in the presence of sodium ethoxide.

General Procedure for the Preparation of 1,3-Benzoxathioles (IIIh-m).

A mixture of ester (IIIa-d) (0.025 mole), ethanol (50 mL) and 4% aqueous sodium hydroxide (38 ml.) was refluxed for 1 hour. The solution was concentrated *in vacuo* (55°) and the concentrate was acidified with 10% hydrogen chloride. The precipitate was filtered off, washed thoroughly with water and *vacuum* dried. Recrystallization from the solvent shown in Table IV yielded the 1,3-benzoxathiole-2-acetic acids (IIIh-m).

Melting points, yields, analytical data and physical properties of the products are listed in Tables IV and V.

General Preparation of the 1,3-Benzoxathioles (XIa-b).

To a suspension of lithium aluminum hydride (0.0026 mole) in anhydrous ether (25 ml.), with stirring, under nitrogen, a solution of the compound VIa (or VIe) (0.005 mole) in anhydrous ether (10 ml.) was added. Subsequently, the mixture was heated under reflux for 30 minutes, cooled, treated with ethyl acetate (1 ml.) and then poured on crushed ice. Following the addition of 20% aqueous hydrochloric acid (1 ml.), the product was isolated *via* ether extraction.

Boiling points, yields, analytical data and physical properties of the products are listed in Tables IV and V.

Acknowledgment.

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